Publications du centre de référence des maladies rares de la peau et des muqueuses d'origine génétique - Année 2019

- Reverse Phenotyping in Patients with Skin Capillary Malformations and Mosaic GNAQ or GNA11 Mutations Defines a Clinical Spectrum with Genotype-Phenotype Correlation. Jordan M, Carmignac V, Sorlin A, Kuentz P, Albuisson J, Borradori L, Bourrat E, Boute O, Bukvic N, Bursztejn AC, Chiaverini C, Delobel B, Fournet M, Martel J, Goldenberg A, Hadj-Rabia S, Mahé A, Maruani A, Mazereeuw J, Mignot C, Morice-Picard F, Moutard ML, Petit F, Pasteur J, Phan A, Whalen S, Willems M, Philippe C, Vabres P. *J Invest Dermatol*, 2019 [in press]

- Management of congenital ichthyoses: European guidelines of care, part one. Mazereeuw-Hautier J, Vahlquist A, Traupe H, Bygum A, Amaro C, Aldwin M, Audouze A, Bodemer C, Bourrat E, Diociaiuti A, Dolenc-Voljc M, Dreyfus I, El Hachem M, Fischer J, Gånemo A, Gouveia C, Gruber R, Hadj-Rabia S, Hohl D, Jonca N, Ezzedine K, Maier D, Malhotra R, Rodriguez M, Ott H, Paige DG, Pietrzak A, Poot F, Schmuth M, Sitek JC, Steijlen P, Wehr G, Moreen M, O'Toole EA, Oji V, Hernandez-Martin A. *Br J Dermatol*, 2019; 180, 272-281

  Abstract
  These guidelines for the management of congenital ichthyoses have been developed by a multidisciplinary group of European experts following a systematic review of the current literature, an expert conference held in Toulouse in 2016 and a consensus on the discussions. They summarize evidence and expert-based recommendations and are intended to help clinicians with the management of these rare and often complex diseases. These guidelines comprise two sections. This is part one, covering topical therapies, systemic therapies, psychosocial management, communicating the diagnosis and genetic counselling.

  Management of congenital ichthyoses: European guidelines of care, part two. Mazereeuw-Hautier J, Hernández-Martín A, O'Toole EA, Bygum A, Amaro C, Aldwin M, Audouze A, Bodemer C, Bourrat E, Diociaiuti A, Dolenc-Voljč M, Dreyfus I, El Hachem M, Fischer J, Ganemo A, Gouveia C, Gruber R, Hadj-Rabia S, Hohl D, Jonca N, Ezzedine K, Maier D, Malhotra R, Rodriguez M, Ott H, Paige DG, Pietrzak A, Poot F, Schmuth M, Sitek JC, Steijlen P, Wehr G, Moreen M, Vahlquist A, Traupe H, Oji V. *Br J Dermatol*, 2019; 180, 484-495

  Abstract
  These guidelines for the management of congenital ichthyoses have been developed by a multidisciplinary group of European experts following a systematic review of the current literature, an expert conference held in Toulouse in 2016, and a consensus on the discussions. These guidelines summarize evidence and expert-based recommendations and intend to help clinicians with the management of these rare and often complex diseases. These guidelines comprise two sections. This is part two, covering the management of complications and the particularities of some forms of congenital ichthyosis.

- Epidermolysis bullosa simplex generalized severe induces a T helper 17 response and is improved by apremilast treatment. Castela E, Tulic MK, Rozières A, Bourrat E, Nicolas JF, Kanitakis J, Vabres P, Bessis D, Mazereeuw J, Morice-Picard F, Baty D, Berard F, Lacour JP, Passeron T, Chiaverini C. *Br J Dermatol*, 2019; 180, 357-364

Abstract

BACKGROUND: Epidermolysis bullosa simplex generalized severe (EBS-gen sev) is a genetic disorder caused by mutation in the KRT5 or KRT14 genes. Although it is usually considered a mechanical disease, recent data argue for additional inflammatory mechanisms.

OBJECTIVES: To assess the inflammation in the skin of patients with EBS-gen sev.

METHODS: A first immunohistochemical retrospective study was performed on frozen skin samples from 17 patients with EBS-gen sev. A second multicentre prospective study was conducted on 10 patients with severe EBS-gen sev. Blister fluid and epidermis were processed for immunochemical analysis and quantitative real-time polymerase chain reaction. Cytokine expression was analysed in blister fluid and compared with that in controls.

RESULTS: Histological analysis showed a constant dermal perivascular $CD4^+$ lymphocyte infiltrate in skin biopsies of both blister (n = 17) and rubbed skin (n = 5), an epidermal infiltration of neutrophils and eosinophils in 70% of cases, and increased immunostaining for CXCL9 and CXCL10 in blistering skin. High levels of T helper 17 cytokines were detected in lesional skin. Three adult patients with EBS-gen sev were treated with apremilast, with a dramatic improvement of skin blistering and good tolerance.

CONCLUSIONS: Our study demonstrates the importance of inflammation in patients with EBS-gen sev and underlines the key role for T helper 17 cells in its pathogenesis. In addition, this study provides promising new therapeutic approaches for this disabling disorder.

- Dermatological manifestations in cardiofaciocutaneous syndrome: a prospective multicentric study of 45 mutation-positive patients. Bessis D, Morice-Picard F, Bourrat E, Abadie C, Aouinti S, Baumann C, Best M, Bursztejn AC, Capri Y, Chiaverini C, Coubes C, Giuliano F, Hadj-Rabia S, Jacquemont ML, Lacombe D, Lyonnet S, Mallet S, Mazereeuw-Hautier J, Miquel J, Molinari N, Parfait B, Pernet C, Philip N, Pinson L, Pouvreau N, Vial Y, Sarda P, Sigaudy S, Verloes A, Cavé H, Geneviève D. *Br J Dermatol*, 2019; 180, 172-180

Abstract

BACKGROUND: Data on dermatological manifestations of cardiofaciocutaneous syndrome (CFCS) remain heterogeneous and almost without expert dermatological classification.

OBJECTIVES: To describe the dermatological manifestations of CFCS; to compare them with the literature findings; to assess those discriminating CFCS from other RASopathies, including Noonan syndrome (NS) and Costello syndrome (CS); and to test for dermatological phenotype-genotype correlations.

METHODS: We performed a 4-year, large, prospective, multicentric, collaborative dermatological and genetic study.

RESULTS: Forty-five patients were enrolled. Hair abnormalities were ubiquitous, including scarcity or absence of eyebrows and wavy or curly hair in 73% and 69% of patients, respectively. Keratosis pilaris (KP), ulerythema ophryogenes (UO), palmoplantar hyperkeratosis (PPHK) and multiple melanocytic naevi (MMN; over 50 naevi) were noted in 82%, 44%, 27% and 29% of patients, respectively. Scarcity or absence of eyebrows, association of UO and PPHK, diffuse KP and MMN best differentiated CFCS from NS and CS. Oral acitretin may be highly beneficial for therapeutic management of PPHK, whereas treatment of UO by topical sirolimus 1% failed. No significant dermatological phenotype-genotype correlation was determined.

CONCLUSIONS: A thorough knowledge of CFCS skin manifestations would help in making a positive diagnosis and differentiating CFCS from CS and NS.

- Dermatological manifestations in Noonan syndrome: a prospective multicentric study of 129 patients positive for mutation. Bessis D, Miquel J, Bourrat E, Chiaverini C, Morice-Picard F, Abadie C, Manna F, Baumann C, Best M, Blanchet P, Bursztejn AC, Capri Y, Coubes C, Giuliano F, Guillaumont S, Hadj-Rabia S, Jacquemont ML, Jeandel C, Lacombe D, Mallet S, Mazereeuw-Hautier J, Molinari N, Pallure V, Pernet C, Philip N, Pinson L, Sarda P, Sigaudy S, Vial Y, Willems M, Geneviève D, Verloes A, Cavé H. *Br J Dermatol*, 2019; 180, 1438-1448

Abstract

BACKGROUND: Data on dermatological manifestations of Noonan syndrome (NS) remain heterogeneous and are based on limited dermatological expertise.

OBJECTIVES: To describe the dermatological manifestations of NS, compare them with the literature findings, and test for dermatological phenotype-genotype correlations with or without the presence of PTPN11 mutations.

METHODS: We performed a large 4-year, prospective, multicentric, collaborative dermatological and genetic study.

RESULTS: Overall, 129 patients with NS were enrolled, including 65 patients with PTPN11-NS, 34 patients with PTPN11-NS with multiple lentigines (NSML), and 30 patients with NS who had a mutation other than PTPN11. Easy bruising was the most frequent dermatological finding in PTPN11-NS, present in 53·8% of patients. Multiple lentigines and café-au-lait macules (n ≥ 3) were present in 94% and 80% of cases of NSML linked to specific mutations of PTPN11, respectively. Atypical forms of NSML could be associated with NS with RAF1 or NRAS mutations. In univariate analysis, patients without a PTPN11 mutation showed (i) a significantly higher frequency of keratinization disorders (P = 0·001), including keratosis pilaris (P = 0·005), ulerythema ophryogenes (P = 0·0001) and palmar and/or plantar hyperkeratosis (P = 0·06, trend association), and (ii) a significantly higher frequency of scarce scalp hair (P = 0·035) and scarce or absent eyelashes (P = 0·06, trend association) than those with PTPN11 mutations.

CONCLUSIONS: The cutaneous phenotype of NS with a PTPN11 mutation is generally mild and nonspecific, whereas the absence of a PTPN11 mutation is associated with a high frequency of keratinization disorders and hair abnormalities.

- Burden of itch in ichthyosis: a multicentre study in 94 patients. De Palma AM, Mazereeuw-Hautier J, Giehl K, Hernández-Martin A, Merlos M, Moons P, Morren MA. *J Eur Acad Dermatol Venereol*, 2019; 33, 2095-2100

Abstract

BACKGROUND: From clinical experience, we know that itch is a major concern for many ichthyosis patients. Nonetheless, no previous studies specifically addressed the issue of itch in ichthyosis.

OBJECTIVE: The objective of this study was to specifically address the burden of itch and all its dimensions in ichthyosis patients.

METHODS: Ninety-four ichthyosis patients from four different centres were recruited to participate in this cross-sectional, questionnaire-based study. All participants completed the Leuven Itch Scale, a multidimensional self-report instrument that quantifies the frequency, duration, severity, distress, consequences and surface area of itch.

RESULTS: Participants included 18 keratinopathic types, 55 autosomal recessive congenital ichthyoses, 11 X-linked recessive ichthyoses (XLRIs), 6 Netherton's ichthyoses, 1 Sjögren-Larsson type, 1 locrin ichthyosis and 2 unknown subtypes. Itch occurred in 93% of all patients. In patients with itch, 63% reported that it was often or always present, although most itch episodes were short in duration. Itch, in all its dimensions, was worst in patients with Netherton syndrome. Patients with XLRI had in general a lower itch profile. About half of all ichthyosis patients reported to experience flares during a change in weather, in a hot environment or in stressful situations, whereas a cold environment led to itch in only 26% of patients. The most significant consequences of itching were lesions from scratching, difficulties in falling asleep, bad mood and loss of concentration.

CONCLUSIONS: Itch is a major concern in patients with ichthyosis, with significant impact on daily life. Research on future treatments should therefore take itch into consideration and itch should be evaluated in clinical studies. Among the studied subgroups, Netherton patients experienced the most severe consequences.

- Segmental schwannomatosis: characteristics in 12 patients. Alaidarous A, Parfait B, Ferkal S, Cohen J, Wolkenstein P, Mazereeuw-Hautier J. *Orphanet J Rare Dis*, 2019; 14, 207

Abstract

BACKGROUND: Segmental schwannomatosis is characterized by multiple schwannomas affecting one-limb or less than 5 contiguous segments of spine. Its characteristics are not well described in the literature. Our objective was to better describe the demographic and clinical characteristics of this condition.

METHODS: This was a retrospective, bi-center study conducted in two French expert centers for neurofibromatosis and schwannomatosis. The clinical, radiographic, pathological and molecular aspects were extracted from patients' clinical records.

RESULTS: Twelve patients with segmental schwannomatosis were identified. Eight were female and 4 were male. The median age at initial symptom was 29 years (range: 6-60 years) and the median age at diagnosis was 34.5 years (range: 13-65 years). Pain was the initial symptom for the majority of patients (7 of 12). The number of tumors was variable with six patients having more than 10 tumors. Peripheral distribution was seen in all patients. Quality of life could be impaired (median Dermatology Life Quality Index score was 4.5 (range: 2-13). The median duration of follow up was 3 years (range: 1-26). Chronic pain was the main complication (9 of 12 patients). Surgical intervention to control chronic pain was performed for 9 patients of whom 5 experienced recurrence of tumors. Molecular investigations revealed heterozygous LZTR1 variants in 3 of 9 patients.

CONCLUSION: Segmental schwannomatosis is a rare condition that may start early in life and often remains undiagnosed for many years. Pain is the main symptom and consequently could impair the quality of life. Surgery seems to be effective, but recurrences are frequent. Some patients carried heterozygous LZTR1 variants. Further studies are needed to better understand this rare condition.

- Effect of Topical Rapamycin 1% on Multiple Trichoepitheliomas. Dreyfus I, Onnis G, Tournier E, Dereure O, Mazereeuw-Hautier J. *Acta Derm Venereol*, 2019 ; 99, 454-455

- Clinical Profile of Methotrexate-resistant Juvenile Localised Scleroderma. Hardy J, Boralevi F, Mallet S, Cabrera N, Belot A, Phan A, Barbarot S, Duriez-Lasek A, Chiaverini C, Hubiche T, Mahé E, Bégon E, Bourrat E, Boccara O, Aubert H, Lerosey MG, Droitcourt C, Piram M, Mazereeuw-Hautier J; Research Group of the French Society of Paediatric Dermatology (SDFP in French). *Acta Derm Venereol*, 2019; 99, 539-543

Abstract
Methotrexate has demonstrated its efficiency for the treatment of juvenile localized scleroderma but some patients may be resistant. The aim of our study was to define the profile of such patients. We performed an observational retrospective multicenter study between 2007 and 2016 and included all children seen in the French Paediatric Dermatology and Rheumatology departments with active localized scleroderma treated by methotrexate for a minimum of 4 months. Metho-trexate efficacy was assessed clinically and/or by imaging between the fourth to twelfth months of treatment. A total of 57 patients were included. Metho-trexate dosage ranged from 7 to 15 mg/m2/week. Only 4 patients were resistant. No common features could be identified between these 4 patients. Children with localized scleroderma are rarely resistant to metho-trexate and we did not identify a clinical profile for those resistant patients.

- Keratitis-Ichthyosis-Deafness Syndrome: Early Death Caused by the GJB2 Mutation p.Gly12Arg. Godillot C, Severino-Freire M, Michaud V, Boralevi F, Labrèze C, Guigonis V, Onnis G, Morice-Picard F, Mazereeuw-Hautier J. *Acta Derm Venereol*, 2019; 99, 921-922

- Topical sirolimus 0.1% for treating cutaneous microcystic lymphatic malformations in children and adults (TOPICAL): protocol for a multicenter phase 2, within-person, randomized, double-blind, vehicle-controlled clinical trial. Leducq S, Caille A, Barbarot S, Bénéton N, Bessis D, Boccara O, Bursztejn AC, Chiaverini C, Dompmartin A, Droitcourt C, Gissot V, Goga D, Guibaud L, Herbreteau D, Le Touze A, Léauté-Labrèze C, Lorette G, Mallet S, Martin L, Mazereeuw-Hautier J, Phan A, Plantin P, Quéré I, Vabres P, Bourgoin H, Giraudeau B, Maruani A; Groupe de Recherche de la Société Française de Dermatologie Pédiatrique. *Trials*, 2019 ; 20, 739

Abstract
BACKGROUND: Cutaneous microcystic lymphatic malformations (CMLMs) are rare conditions in children and adults. They present as clusters of vesicles full of lymph and blood to various extents, inducing maceration, esthetic impairment, pain, and impaired quality of life. The treatment is challenging. Sirolimus is an inhibitor of mammalian target of rapamycin (mTOR) involved in angio-lymphangiogenesis. Topical sirolimus has recently been reported as effective in a few reports of patients with CMLMs. The objective is to compare the efficacy and safety of a 12-week application of 0.1% topical sirolimus versus topical vehicle in CMLMs in children and adults.

METHODS: This French blinded multicenter within-person randomized controlled phase 2 trial aims to include 55 patients aged ≥ 6 years who have a primary CMLM. The CMLM will be divided into two equal areas that will be randomly allocated to 0.1% topical sirolimus or topical vehicle applied for 12 weeks. At the end of the 12-week period, the patient/parent will treat the whole area of CMLM with 0.1% topical sirolimus on remaining lesions, for eight more weeks. Patients will be seen at week 20 (treatment will be stopped) and at month 12 to evaluate long-term efficacy. The primary outcome will be improvement of the CMLM in the area treated with topical sirolimus compared to the area treated with topical vehicle by the investigator physician (blinded to the treatment) with the Physician Global Assessment score at week 12. Secondary outcomes will include: assessment of efficacy by independent experts on the basis of standardized photographs; impact on quality of life; efficacy for oozing, bleeding, erythema, and thickness evaluated by the investigators; and global efficacy as well as efficacy for functional and aesthetic impairment evaluated by the patient. Systemic passage of sirolimus will be measured at weeks 6, 12, and 20, and at week 16 for CMLMs ≥ 900 cm^2.

DISCUSSION: For patients with CMLMs, topical sirolimus could be a non-invasive and well-tolerated therapeutic option. If the trial demonstrates efficacy and safety of this treatment, this result will lead to a real change in the management of this condition, and 0.1% sirolimus cream would become the first-line treatment.

TRIAL REGISTRATION: ClinicalTrials.gov, NCT03972592. Registered on 3 June 2019. EU Clinical Trials Register EudraCT, 2018-001359-11.

- Severe gynaecological involvement in Proteus Syndrome. Severino-Freire M, Maza A, Kuentz P, Duffourd Y, Faivre L, Brazet E, Chassaing N, Mery-Lemarche E, Vabres P, Mazereeuw-Hautier J. *Eur J Med Genet*, 2019; 62, 270-272

Abstract
Proteus Syndrome is a rare complex overgrowth syndrome. We report a young female patient with Proteus Syndrome due to AKT1 mutation c.49G > A (p.Glu17Lys), presenting with a severe gynaecological involvement which necessitated a complete hysterectomy and a left adnexectomy. Cases of gynecological involvements in Proteus Syndrome are rare, not well known by physicians while they can be potentially severe.

- Acanthosis nigricans, hypochondroplasia, and FGFR3 mutations: Findings with five new patients, and a review of the literature. Muguet Guenot L, Aubert H, Isidor B, Toutain A, Mazereeuw-Hautier J, Collet C, Bourrat E, Denis Musquer M, Barbarot S; Groupe de Recherche de la Société Française de Dermatologie Pédiatrique. *Pediatr Dermatol*, 2019 ; 36, 242-246

Abstract
Early development of extensive acanthosis nigricans (AN) is a key feature in some patients who have hypochondroplasia (HCH) in association with FGFR3 mutations. We here report regarding five new patients with HCH who exhibited AN, and we compare their characteristics to the eight patients previously described in the literature. In these patients, the AN lesions began in childhood, and they were extensive. These lesions were located on the torso, the abdomen, and the face, in addition to the typical skin fold sites. Other skin lesions were frequently reported: café-au-lait macules, melanocytic nevi, lentigines, and seborrheic keratosis. The Lys650Thr mutation was the predominant reported mutation of FGFR3.

- Why is it so difficult for GPs to effectively manage patients with rare skin diseases? Baqué M, Colineaux H, Dreyfus I, Mesthé P, Mazereeuw-Hautier J. *Presse Med*, 2019, 48, e382-e388

Abstract
BACKGROUND: Rare diseases are defined by a prevalence of less than one out of 2000 persons. In clinical practice, their management is difficult, due to their diversity, their complexity and a lack of adapted physician training.

OBJECTIVE: The aims of this study were to identify rare skin diseases in a reference center, to describe the difficulties encountered by general practitioners (GPs) in management of these uncommon cases, and to pinpoint the characteristics of the GPs having the most problems.

METHODS: A survey conducted from March to June 2017 involving GPs at least one of whose rare skin disease patients was being monitored in a reference center.

RESULTS: All in all, 96/195 (49.2%) of the GPs contacted completed the questionnaire, and virtually all of them (95%) reported five main categories of difficulties: giving a diagnosis, monitoring treatment, coordinating care, providing support, and ensuring management of intercurrent pathologies. The most widely reported difficulties were related to diagnosis (88.5%) and care coordination (76%). The GPs most in need of assistance were those practicing in rural areas (11 times more likely to experience difficulties), those with over 10 years of experience (up to 9.8 times more risk) and those not considering their role in the management of patients with rare diseases as instrumental (2.28 times more risk).

CONCLUSIONS: This study brought to light the difficulties encountered by GPs in management of patients with rare skin diseases. We identified those the most in need of assistance, who are to be targeted for actions aimed at improving the care and treatment of patients suffering from rare skin diseases.

- Activography reveals aberrant proteolysis in desquamating diseases of differing backgrounds. Zingkou E, Pampalakis G, Kiritsi D, Valari M, Jonca N, Sotiropoulou G. *Exp Dermatol*. 2019; 28: 86-89.

Abstract
The role of epidermal proteolysis in overdesquamation was revealed in Netherton syndrome, a rare ichthyosis due to genetic deficiency of the LEKTI inhibitor of serine proteases. Recently, we developed activography, a new histochemical method, to spatially localize and semiquantitatively assess proteolytic activities using activity-based probes. Activography provides specificity and versatility compared to in situ zymography, the only available method to determine enzymatic activities in tissue biopsies. Here, activography was validated in skin biopsies obtained from an array of distinct disorders and compared with in situ zymography. Activography provides a methodological advancement due to its simplicity and specificity and can be readily adapted as a routine diagnostic assay. Interestingly, the levels of epidermal proteolysis correlated with the degree of desquamation independent of skin pathology. Thus, deregulated epidermal proteolysis likely represents a universal mechanism underlying aberrant desquamation.